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Award Number: W81XWH-05-1-0056

TITLE: Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

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REPORT DATE: January 2007

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
01-01-2007	Final	20 Dec 2004 – 19 Dec 2006

4. TITLE AND SUBTITLE

Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-05-1-0056

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The Queen's Medical Center
Honolulu, HI 96813-2413

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
Original contains colored plates: ALL DTIC reproductions will be in black and white.

14. ABSTRACT

The purpose of this project is to develop and evaluate fluorine-18 (F-18) fluorocholine (FCH) positron emission tomography (PET) as an imaging technique that can be used to delineate malignant tumors in the prostate gland. The proposed technique works by measuring the tissue metabolism of FCH, a substrate that is preferentially metabolized by cancer cells due to malignant over-expression of the choline transporter and choline kinase enzyme. The project scope covers a clinical study to recruit men with prostate cancer who have elected treatment by radical prostatectomy surgery. These men will undergo pre-operative PET scanning to measure F-18 FCH uptake in anatomical sextants of the prostate gland. Imaging results will be compared to histopathologic analyses of the prostatectomy specimen to determine the accuracy of F-18 FCH PET for detecting cancerous prostate sextants. Magnetic resonance microscopy (MRM) followed by complete embedding and close step-sectioning of specimens will produce the histopathologic standard of reference for this study. Based on data collected from 15 subjects so far, the diagnostic sensitivity and specificity of FCH PET for identifying malignant prostate sextants is estimated at 85% and 62% respectively. Because recent technological advances in PET and computerized tomography (CT) may improve accuracy further, the project is being revised to capitalize on the new features of two PET/CT scanners to be installed at the contract performing organizations in 2007. This revision is expected to enhance the clinical relevance of the final study results. Project completion will require a one-year no-cost extension. To support this change in project scope, we report: 1) an interim analysis of the data, 2) a Study on the feasibility of FCH PET/CT guided prostate radiation therapy, and 3) the application of new PET imaging techniques (list-mode and time-of-flight PET) to prostate imaging.

15. SUBJECT TERMS
Prostate Cancer, Localization, Positron Emission Tomography, Fluorocholine

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	31	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION

Prostate cancer is the second leading cause of cancer death in American men over 50 years of age. Ultrasound-guided prostate biopsy is currently the most common method for diagnosing and localizing cancer in the prostate. However, even when standard 6 or 12 needle biopsy templates are used, this technique is prone to sampling error. Its false negative rate has been estimated to be as high as 20% regardless of the number of needles employed *(1, 2)*. While progress has been made in the detection of primary prostate cancer using imaging techniques such as ultrasound and magnetic resonance imaging, not all of the technical hurdles associated with these non-invasive imaging techniques have been overcome *(3)*.

Positron emission tomography offers an alternative approach to detecting tumors through the measurement of metabolic changes at the cellular level. This technique works by depicting the biochemical interactions of radiolabeled tracers within the body. Fluorine-18 fluorocholine (FCH) is a recently developed tracer that allows positron emission tomography (PET) to image choline metabolism in-vivo. The observation that there is increased choline metabolism in malignant prostate tissue relative to normal tissue supports the possibility of using F-18 FCH PET for visualizing cancer in the prostate gland.

The primary objective of this project is to develop and evaluate F-18 FCH PET as a method for identifying the presence of malignancy in anatomical sextants of the prostate gland. To meet this objective, a clinical study was designed to recruit 25 subjects with organ-confined prostate cancer to undergo PET scanning with FCH prior to planned radical prostatectomy (surgical removal of the prostate) for the treatment of their disease. The prostate specimens collected in this study would then be used to provide the diagnostic reference for determining the accuracy of FCH PET for sextant-based detection of prostate malignancy.

BODY

STUDY PREPARATION (related to SOW Task 1)

In the first year of the award, we established a multicenter collaboration between the Armed Forces Institute of Pathology (AFIP), Tripler Army Medical Center (TAMC), and the Queen's Medical Center (QMC) through a cooperative research and development agreement (CRDA) with the Department of Defense Clinical Investigation Regulatory Office (Federal Laboratory). The availability of TAMC and QMC as 2 clinical sites from which subjects could be recruited provided an opportunity to study two distinctly different groups of prostate cancer patients in the state of Hawaii. The patients from QMC were older and reflective of Hawaii's ethnically diverse population, while the patients from TAMC were younger and have undergone more frequent medical screening. The role of the AFIP in this study was to perform detailed histopathologic analysis of prostate specimens using histopathologic techniques not available at QMC or TAMC. These techniques include complete embedding and step sectioning of the whole prostate specimen, as well as immunohistochemical staining of tissue specimens for the Ki-67 antigen (a marker of proliferation). For this study, a protocol was established to perform FCH PET imaging at QMC, surgery at QMC or TAMC, and histopathologic analysis at AFIP.

Before commencement of the clinical study, a human subjects protocol review was conducted by each clinical site's institutional review board (IRB) as well as the Department of the Defense Human Subjects Research and Review Board (HSRRB). After second-tier review by the HSRRB was completed in December 2004, study personnel at all sites were briefed on the procedures of the study. The completion of these activities constitutes fulfillment of Statement of Work (SOW) Task 1. The study protocol is subject to continuing review on an annual basis by both local IRBs and the HSRRB. The protocol is currently approved until 31 July 2007 at QMC and until 24 Oct 2007 at TAMC. The protocol underwent one revision during the course of the study. In November 2005, a revision to the study inclusion criteria was made based on observations made in the initial 5 subjects. Originally, only subjects with less than two-thirds cancer involvement of their biopsy specimens were allowed to participate in the study. This was done to exclude subjects with

very large tumor volumes since subjects with large tumors were not felt to be representative of patients who would require sensitive imaging techniques for prostate tumor localization. However, as described in the project's 2005 annual report, the initial subjects recruited from TAMC were found to have extremely low tumor volumes. The average total tumor volume by step-section analysis of specimens from TAMC was 3.7 cc (range 0.03 cc to 5.7 cc), which was significantly lower than the average tumor volume of 8.3 cc (range 0.2 cc to 28.7 cc) in prostates obtained from subjects recruited from QMC ($p < 0.05$). The average mass of prostate specimens from TAMC was also significantly less than those from QMC (average mass, 48 g vs. 62 g, $p < 0.05$). Out of concern that very low tumor volumes could unfairly impact the accuracy of FCH PET, a protocol revision was made to remove the criteria limiting the amount of malignancy that could be found on biopsy. In the revised protocol, subjects are only required to have clinically organ-confined prostate cancer (Stage II) for which they have elected treatment by radical prostatectomy.

STUDY METHODS (relevant to SOW Tasks 2 and 3)

Radioactive Tracer Synthesis

The radioactive tracer 18F- FCH was synthesized in accordance with a synthesis method described in Food and Drug Administration (FDA) Investigational New Drug (IND) application #66,319. Synthesis of the product was performed by fluorination of ditosylmethane with fluorine-18 followed by alkylation of fluorotosylmethane with dimethylethanolamine. The synthesis procedure was automated and performed at an on-site cyclotron laboratory at QMC using a computer controlled chemical process control unit (CTI/Siemens CPCU, CTI/Siemens, Knoxville, TN) *(4)*. All products passed assays for radiochemical purity, radionuclidic identity, chemical purity, sterility and pyrogenicity in compliance with United States Pharmacopia (USP) Good Clinical Practice (GCP) guidelines.

PET Imaging

Following written informed consent, PET was performed at QMC using a Hamamatsu SHR-22000 PET Instrument (Hamamatsu Photonics KK, Hamamatsu City, Japan). For PET scanning, subjects were positioned lying supine in the PET scanner. Whole-body transmission scans were acquired using two Germanium-68 rod sources over 5 fields of view (FOVs) . Three minute transmission scans were performed at each FOV. A dose of 3.3 to 4 Mbq/kg of 18F- FCH was administered intravenously following the transmission scans. After a delay of approximately 10 minutes, 2D emission scans were acquired over the same FOVs for 7 minutes each beginning at the level of the pubic symphysis and proceeding cephalad. The PET images were reconstructed using an ordered subsets expectation maximization algorithm. Segmented attenuation correction was applied to the emission data using the measured transmission data. Reconstruction resulted in 4mm by 4mm by 3.6 mm voxels. Images were viewed and analyzed on a nuclear medicine imaging workstation (Medasys Data Systems, Gif-sur-Yvete Cedex, France) (Figure 1).

The protocol used in this study differs on an important point from a protocol used in a recent study that evaluated both whole-body and prostate scanning with FCH PET/CT *(5)*. This other study performed prostate imaging at 2 minutes after the intravenous injection of FCH. In contrast, we begin imaging at 10 minutes post-injection based on observations that the ratio of tumor-to-background uptake of FCH in the prostate continues to improve after 10 minutes*(6)*.

Computerized Tomography of the Pelvis

Immediately following PET, computed tomography (CT) of the pelvis was performed using a conventional CT scanner. The role of CT was to provide anatomical sextant correlation for the PET images. The CT images were registered to PET using a commercial image registration software package (HERMES, Hermes Medical Solutions, Battle Ground, WA). Images were provided in DICOM format for review and analysis on a workstation.

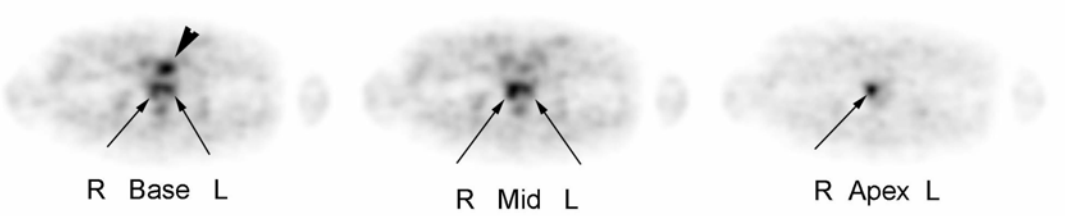


Figure 1: FCH PET Images of the Prostate. In this example, a malignant tumor demonstrates increased FCH uptake from the base to apex of the prostate (long arrows point to malignant prostate sextants). Urinary excretion of FCH is evident in the urinary bladder (large arrowhead).

Image Analysis

PET images were visually evaluated by two independent readers (S.K., M.C.) for the presence of tracer uptake in the prostate. Both readers have previous experience with the interpretation of FCH PET images *(7, 8)*. The readers were blinded to the histopathology results at initial reading. The prostate on FCH PET can be seen as a discrete region of uptake located inferior and slightly posterior to the urinary bladder (Figure 1). With software registration of PET and CT images, slight image mis-registrations were expected (due to changes in organ shape over the time between PET and CT). However, the fused PET and CT images were still useful for confirming the configuration of the prostate gland. A PET/CT scanning device, if one was available at the time, would have simplified the identification of prostate sextants.

The measurement of uptake in prostate sextants proceeded as follows: Visualized prostate volumes were segmented according to a sextant biopsy template into an upper (basal) one-third, middle one-third, and lower (apical) one-third portion on each side. Using region of interest (ROI) analysis, the prostate sextant region with highest FCH Uptake was identified. The maximum standardized uptake value (SUVmax) of all sextants was recorded. SUVmax was defined as the maximum measured activity divided by the injected radioactivity normalized to body weight. The task of identifying the prostate gland and the prostate sextant region with highest uptake was aided by the relatively consistent position of the prostate in the pelvis, and its higher uptake relative to surrounding pelvic structures at the same level. In each case, there was reader-agreement and concordance in ROI-measured SUVmax.

Prostate Specimen Procurement and Analysis

After surgery, intact prostate specimens were placed in a 10% formalin solution for 2 to 3 days. The fixed specimens were then packaged securely and shipped to AFIP. Upon receipt by AFIP, the specimen was inspected by a technician and submitted for imaging at 7 telsla using a magnetic resonance microscope(MRM) (Bruker Biospec 7T, Bruker Biopsin Corp, Billerica, MA). Three-dimensional datasets of the entire organ and quantitative 2D slice images at selected planes were acquired for each specimen using various MRI sequences. The MRM images were obtained as potential templates for identifying the sextant location of tumors in the event there was difficulty in performing retrospective alignment of the specimen slices. However, it turned out that there was little difficulty in grossly determining the 3-dimensional orientation of specimen based on the pathologist's review of the slides. Visual inspection of the slides was sufficient for localizing tumors to within a sextant region. In the future, MRM may prove beneficial for studying sub-sextant localization or performing higher-precision modeling of prostate tumor distributions.

Histologic processing of the prostate specimen was performed by the step-section technique. Completely embedded whole prostate specimens were sectioned at regular 2.2 mm intervals. Thin slices from each section were mounted on large glass slides and stained with hemotoxylin and eosin. Alignment markers were placed on each slide to record the spatial orientation between slices. Areas of malignant tumor on each slide were manually segmented by a a pathologist (I. Sesterhenn). Each slide was photographed to scale using a digital camera mounted on a stage (Figure 2). A report describing the size, Gleason scoring, and sextant location of all malignant tumors was provided for each specimen.

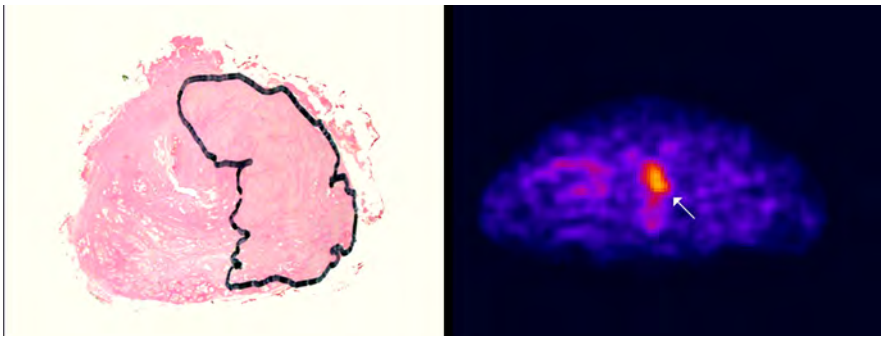


Figure 2: Left: A malignant tumor is outlined in black on this 10X photomicrograph of a prostate specimen. Right: The corresponding prostate gland on this transaxial FCH PET image of the pelvis is located at the center of the image (white arrow). As shown on this image, FCH uptake is increased in the left side of the prostate, which corresponds to the tumor seen in the photomicrograph.

Analysis and Statistical Considerations

The unit of analysis is the prostate sextant. For each sextant, histopathology provides the "true" result signifying the presence or absence of malignancy (either macroscopic as defined by tumor diameter > 0.5cm, or tumor of any size). Diagnostic sensitivity, specificity, and accuracy was calculated for sextant based diagnosis using SUVmax measurements from FCH PET images of the prostate. Sensitivity and specificity as a function of SUVmax were explored by receiver operating characteristic (ROC) analysis. Differences in sample means were tested for significance using Student's t-test. For paired measurements, differences in means were tested for significance using the paired t-test. The linear relationship between two variables was assessed using the Pearson correlation coefficient. Statistical analysis was performed using JMP Version 5 (SAS Institute Inc., Cary, NC). All tests were two-sided and p-values < 0.05 were considered significant.

RESULTS (Related to SOW Task 4)

Patient Characteristics

Between January 1 2005 and May 31 2006, a total of 12 subjects were recruited for the study. Nine subjects were recruited from TAMC and 3 subjects were recruited from QMC. For analysis, data from 3 subjects who took part in a pilot study was also included to increase the statistical power of the study. This data was acquired using the same methodology as the current study. Individual subject characteristics are summarized in Table 1. The average age of subjects was 62 years (range 47 to 71 years). Subjects recruited from TAMC were significantly younger than subjects recruited from QMC (58 years vs. 67 years, $p < 0.01$). The median serum PSA was 5.1 ng/dl (range 3.5 to 13.8 ng/dl). The median Gleason Sum Score was 6 (range 6 to 9). Correlation analysis revealed no significant correlations between highest SUVmax in the prostate, subject's age, serum PSA, and Gleason Sum Score.

Histopathologic Findings

Sixty-one of 90 prostate sextants were found to contain at least one malignant tumor on histopathologic analysis. The median number of malignant sextants was 4 (range 2 to 6). There was evidence of benign prostatic hyperplasia or prostatitis in every prostate examined. The mean total tumor volume was 4.9 cc (range 0.01 cc to 28.77 cc).

Subject	Age (years)	PSA (ng/ml)	Gleason Sum	Prostate Weight (gm)	Total Tumor Volume (ml)	# of Malignant Sextants	Diameter of Largest Tumor (mm)	Sextant SUVmax of Largest Tumor	Highest SUVmax of Prostate
1	58	3.5	3+3	27.67	5.72	5	23	6.9	6.9
2	47	4	3+3	46.30	4.2	6	26	11.3	11.3
3	54	5	3+3	12.88	4.98	3	18	4.9	4.9
4	52	4	4+3	25.80	1.67	4	13	3.5	3.5
5	63	6.5	3+3	104.60	0.03	2	4	4.1	4.1
6	63	5.1	3+4	49.90	0.49	2	9	5.8	5.8
7	57	8.1	3+3	34.20	0.05	3	3	3.2	3.2
8	62	4.2	3+3	33.50	9.30	6	25	4.5	4.5
9	63	7.1	3+3	49.30	1.68	5	20	6.9	6.9
10	62	5	4+5	41.9	14.01	5	33	7.0	7.0
11	71	6.3	3+3	43.6	5.88	6	18	7.3	7.3
12	68	10.2	3+4	36.72	28.71	4	33	7.2	7.2
13	66	3.5	3+3	62.8	1.14	4	16	7.0	7.3
14	67	10	3+3	82.1	0.2	4	5	3.6	4.1
15	66	13.8	3+3	106.1	0.2	4	2	7.1	7.1

Table 1: Characteristics of 15 subjects who underwent FCH PET prior to radical prostatectomy with whole-mount histopathologic analysis of their prostate specimens.

PET Images

For each subject, the highest SUVmax of the prostate and the highest SUVmax corresponding to the sextant with the largest tumor is shown in table 1. For additional detail, the histopathologic findings and SUVmax of each prostate sextant is provided in Table 2 (included in Appendix 2: Supplementary Data). The mean SUVmax of malignant sextants was significantly greater than the mean SUVmax of benign sextants (6.0 vs 3.8 respectively , $p < 0.0001$). In all subjects, the highest SUVmax in the prostate corresponded to a malignant sextant. In 13 out of 15 subjects, the sextant with the highest SUVmax also contained the largest diameter tumor for that specimen. A statistically significant correlation was observed between the maximum diameters of these tumors and sextant SUVmax (Pearson correlation coefficient $r=0.54$, $p < 0.05$).

Accuracy of FCH PET for Identifying Malignant Prostate Sextants

Using a threshhold SUVmax of greater than 4.0 to classify malignantly-involved sextants, sensitivity and specificity of FCH PET was found to be 85% and 62% respectively. Table 3 (included in Appendix 2: Supplementary Data) provides additional information on the sensitivity and specificity of FCH PET at other points on the ROC curve. The area under the ROC curve was 0.82 for FCH PET detection of malignant prostate sextants (Figure 1).

Six out of 9 false-negative sextants contained only tumors smaller than 0.5 cm in diameter. ROC analysis was also performed excluding these tumors. Using the same threshold SUVmax of greater than 4.0 to classify sextants, the sensitivity and specificity of FCH PET for detecting sextants with malignant tumors larger than 0.5 cm was 94% and 60% respectively. The trade-off between sensitivity and specificity is illustrated in Figure 2. For example, when a SUVmax threshold of greater than 5.5 is used to define malignancy, FCH PET will have a sensitivity and specificity of 70% and 80% respectively. Table 4 (included in Appendix 2: Supplementary Data) lists the sensitivity and specificity of FCH PET at all points on the ROC curve. The area under the ROC curve for detecting sextants containing malignant tumors larger than 0.5 cm in diameter is 0.85 (Figure 2).

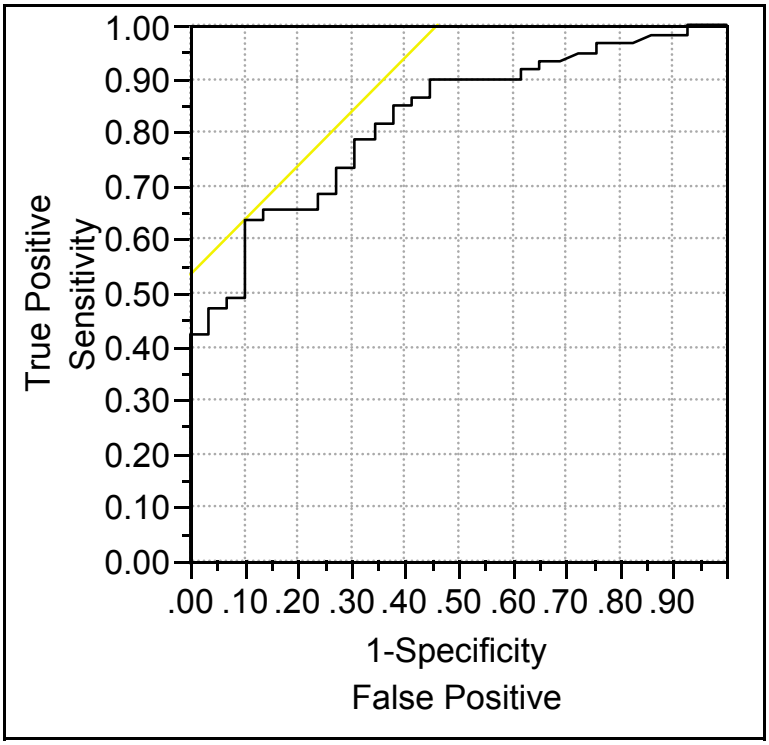


Figure 1. Receiver Operating Characteristic Curve for FCH PET Diagnosis of Malignant Prostate Sextants (regardless of tumor size). Area Under Curve = 0.82.

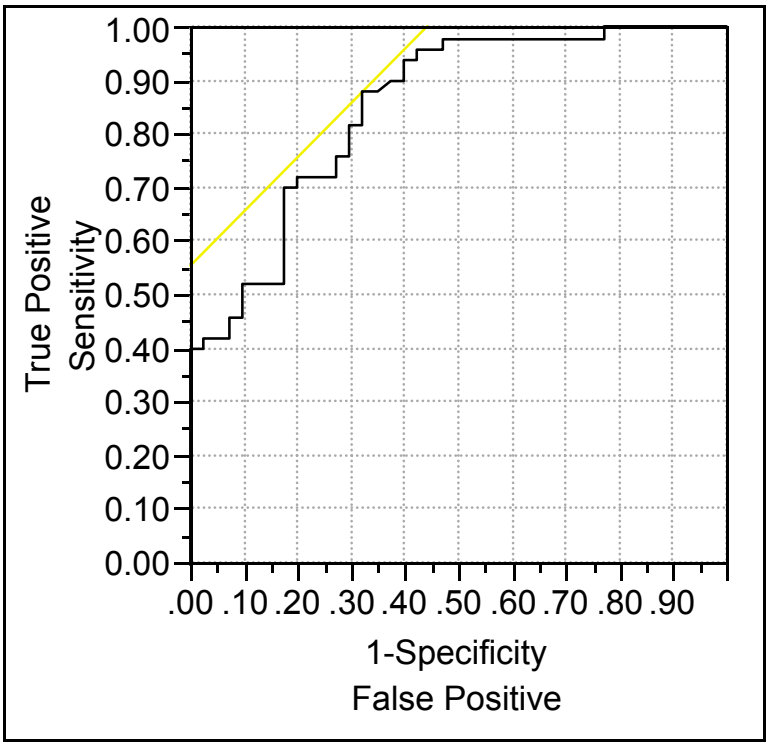


Figure 2. Receiver Operating Characteristic Curve for FCH PET Diagnosis of Sextants Containing Malignant Tumors with > 0.5 cm Diameter. Area Under Curve = 0.85.

DISCUSSION

In our study, FCH PET demonstrates a sensitivity of 85% and specificity of 62% when using a fixed SUVmax threshold to identify prostate sextants containing malignant tumors of any size. Despite the apparent low tumor volumes in the majority of subjects enrolled in this study, this degree of accuracy compares favorably with the accuracy of endorectal MRI/spectroscopy *(9)*, as well as that of digital rectal examination and transrectal ultrasound guided prostate biopsy*(1, 2)*.

In this study, false-negative results were associated with small tumor size. At the 85% sensitivity level, there were 9 false-negative sextants. Of these false-negative sextants, 6 contained only tumors with cross-sectional diameters less than 0.5cm. Furthermore, the diameter of tumors within each sextant correlated well with sextant SUVmax. The effect of size on lesion detectability is not surprising since the measurement of SUV is voxel-based, meaning that it reflects the concentration of radioactivity in a fixed volume of tissue. Assuming there is a higher concentration of FCH in malignant cells, one would expect the measured SUV of a volume containing both malignant and benign cells to be lower than the measured SUV of a volume containing only malignant cells. A recent study that evaluated carbon-11 choline PET for the localization of malignant prostate tumors excluded all tumors smaller than 0.5 cm from their analysis in order to minimize this apparent "partial volume effect"*(10)*. We have analyzed our data with and without the inclusion of tumors smaller than 0.5cm in diameter to provide a comprehensive assessment of sextant-based diagnosis of prostate cancer with FCH PET. As expected, the sensitivity of FCH PET was much higher for detecting only those sextants with malignant lesions having diameters greater than 0.5cm. In light of the favorable prognosis associated with smaller tumors, a diminishing sensitivity for smaller tumors may be clinically acceptable, or even useful since the risks may outweigh the benefits of treatment in some patients with small tumors.

The sextant exhibiting the highest uptake of FCH was found to be malignant in every subject in this study. In 13 out of 15 of these subjects, the sextant with highest uptake was also found to contain the largest tumor in the specimen. Thus, while there is indeed a limit to the size of lesion that can be detected in the prostate with PET, the measurement of FCH uptake in prostate sextants could still point to the area with the highest volume of malignant tumor. Thus, information from FCH PET may have potential value for directing prostate biopsies (to areas of highest malignant potential) or for planning prostate radiation therapy (with the goal of delivering higher radiation doses to the densest area of malignancy).

While these results support FCH as a promising PET probe for primary prostate cancer, the opportunity to potentially improve these results through the use of new PET/CT devices has led us to temporarily postpone completion of the study in anticipation for incorporating PET/CT into the project. Consequently, tasks 2, 3, and 4 of the original SOW have not been completed at this time given that the study is temporarily closed to accrual. The plan and rationale for expanding the scope of this project is outlined in the next section. We hope this change in project scope will serve to protect the clinical relevance of the project by allowing it to keep pace with advancements in imaging technology.

PLAN FOR TO EXPAND THE SCOPE OF WORK IN 2007

During the course of this study from 2004 to 2006, there have been significant advancements in PET imaging technology. These advancements include time-of-flight PET imaging (introduced commercially by Philips Medical Systems in 2006) and hybrid PET/CT. A hybrid PET/CT device consists of a full-ring PET scanner combined with an in-line CT scanner. They are integrated systems capable of providing concurrent images of the body's structure and function. As such, they can provide more accurate anatomical localization of prostate sextants compared to stand-alone PET. In the clinical arena, PET/CT devices have already supplanting previous generation PET scanners for cancer staging and radiation treatment planning. Preliminary data from this project supports the feasibility of applying PET/CT to enhance the effectiveness of prostate radiation therapy.

While PET/CT affords better anatomical localization, time-of-flight PET imaging may have the most potential for improving the quality of prostate images. By increasing the count-rate performance of PET and thus improving image quality (especially in larger patients), time-of-flight imaging should effectively increase the observable contrast between malignant and benign prostate sextants *(11)*. A PET/CT system with time-of-flight capability (Philips Gemini TF PET/CT, Philips Medical Systems, Cincinnati, OH) is going to be installed at The Queen's Medical Center in Summer 2007. We look forward to studying the impact of this device on prostate tumor localization using FCH. A second-generation PET/CT (GE Discovery ST PET/CT, GE Healthcare, Milwaukee, WI) will also be installed at TAMC in April 2007. While this device does not have time-of-flight capabilities, it has the option of operating in 3D mode to produce images with better noise characteristics over our existing PET device (reference: Appendix, Abstract 3). In addition, this device is capable of list-mode data acquisition which will allow for retrospective re-binning of the data to establish optimal time-points at which sextant measurements could be made.

While the most obvious advantage of PET/CT is its ability to provide accurate anatomical correlation for the metabolic images obtained, another clinical advantage to PET/CT is that it can shorten the amount of time needed for scanning by more than 50%. As a result, the test is more tolerable for patients. Also, because a separate CT does not need to be performed immediately following the PET, there is opportunity to perform PET scanning over longer intervals of time to determine whether tumors can be detected based on dynamic changes in FCH uptake within the prostate.

Because the installation of PET/CT devices at TAMC and QMC will begin in Spring and Summer 2007 respectively, a minimum one-year delay in completing this project is expected. We have suspended the recruitment of subjects since May 2006 to guarantee the availability of funding to study additional subjects in 2007. We expect to recruit approximately 13 subjects for PET/CT scanning with FCH at TAMC and QMC. Cost savings (related to reduced procedure costs resulting from no longer having to perform separate PET and CT scans) should provide the funds to study additional subjects or conduct other project activities. While a 6-month project delay was initially requested in July 2006, a one-year extension is currently required as a result of architectural and permitting delays at QMC. An approved SOW reflecting the changes in project scope for 2007 is included in Appendix 1.

KEY RESEARCH ACCOMPLISHMENTS

-The accuracy of FCH PET for prostate sextant diagnosis was reported: Stand-alone PET imaging (ie. without PET/CT), to measure F-18 FCH uptake in prostate sextants was estimated to have a sensitivity of 85% and specificity of 62% for identifying malignant prostate sextants. False-negative results were associated with small-tumor volumes.

-New technologies which may significantly enhance the outcomes of this research project were identified, including hybrid PET/CT, time-of-flight PET imaging, and dynamic imaging with list-mode data acquisition. A one-year no-additional cost extension to the project will allow us to incorporate these advancements, thus expanding the project's scope and enhancing the potential clinical relevance of any subsequent research accomplishments.

-The application of FCH PET/CT to guide and augment radiation therapy to prostate tumors was proven feasible during this project. Using an investigational intensity modulated radiation treatment plan, a high-risk intraprostatic tumor delineated by FCH PET imaging could be given an enhanced radiation dose of 91Gy while the remainder of the gland received a conventional therapeutic dose of 76 Gy. Normal surrounding structures continued to receive a tolerable radiation dose. Thus the potential efficacy of radiation treatment was increased, without necessarily increasing the risk of side-effects from radiation.

REPORTABLE OUTCOMES

Stack R, Thibault R, Kwee S, Furusato B, Potter K, Coel MN, Sesterhenn I. *Comparisons Between Prostate Histopathology and Imaging with 18F-Fluorocholine PET.* the 54th Annual Kimbrough Urological Seminar. January 2007

G. Thibault, R. Stack, S. A. Kwee, B. Furusato, M. Coel and I. Sesterhenn. *Initial Results From a Whole Prostate Histopathologic Correlation Study.*, American Urologic Association – Western Section. Annual Meeting. October 2006.

Kohli V, Kwee SA, Coel MN. *Comparison between 2D and 3D Prostate PET Imaging.* J. Nucl. Med., May 2006; 47: 370P.

Kwee SA, Turner H, Lim J, Wakano C, Coel M. *Dimethylaminoethanol Reduces 18F-Fluoroethylcholine Uptake in Prostate Cancer Cells.* J. Nucl. Med., May 2006; 47: 425P.

Kwee S, Wei H, Sesterhenn IA, Yun DY, Coel MN. *Intensity Modulated Radiation Therapy For Prostate Cancer With Radiation Dose Augmentation Guided By 18F-FCH PET Imaging.* J. Nucl. Med., May 2006; 47: 457P.

Kwee SA, Thibault G, Stack R, Furusato B, Coel M, Sesterhenn IA. *Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study.* J. Nucl. Med., May 2006; 47: 459P.

Kwee SA. et al. *Oncologic Imaging with Fluorine-18 Labeled Choline Derivatives*. Seminars in Nuclear Medicine. Fall 2007 - accepted for publication. Reprint will be submitted upon publication.

SUBSEQUENT PROJECT FUNDING:

"Dynamic PET Study of Prostate Cancer with 18F- Fluorocholine" Philips Medical System Contract for Research Project. In collaboration with the Department of Radiology at The University of Washington and Philips Medical Systems (Bothel, WA). Co-PIs: Sandi Kwee, MD and Manoj Narayanan, PhD.

> Philips Medical Systems is the first manufacturer to implement time-of-flight in a commercially available device. Based on the clinical opportunities supported by our research findings, we have entered into a collaboration with this company to develop clinical applications for FCH PET/CT imaging using time-of-flight. Because FCH kinetic analysis is beyond the current project's scope, a research agreement with Philips Medical Systems and The University of Washington will provide additional expertise to develop potentially non-invasive (ie. no blood sampling required) methods of kinetic parametric analysis suitable for prostate PET imaging with FCH. We should be able to apply this method to the data that we will collect in this study. In addition, Philips has offered to provide technical assistance during implementation of our new PET/CT imaging protocols.

"Measurement of F-18 Choline PET Ligand Uptake and Metabolism in Cultured Human Cancer Cells". Grant from Queen Emma Research Foundation. PI: Sandi Kwee, MD.

PERSONNEL SUPPORTED WITH FUNDS FROM THE RESEARCH PROJECT:

Sandi A. Kwee, MD	Principal Investigator
Marc N. Coel, MD	Co-Investigator
Isabel Sesterhenn, MD	Limited to Payment for Services Rendered through AFIP
Richard Stack, MD	Limited to DoD Approved Reimbursement for Travel Expenses
Gregory Thibault, MD	Limited to DoD Approved Reimbursement for Travel Expenses

CONCLUSION

The results of this project supports FCH PET as an imaging technique to delineate malignant involvement of the prostate gland. In every patient studied, the prostate sextant associated with the highest degree of F-18 FCH uptake was found by histopathologic analysis to contain malignant tumors. Furthermore, the feasibility of applying FCH PET to guide and enhance prostate radiation therapy was demonstrated in this project. Project efforts led to the development of an investigational radiation treatment plan whereby the malignant portion of the prostate gland (delineated by FCH PET) could receive a 20% higher radiation dose than the remainder of the prostate gland, without significantly increasing the side-effect profile of the treatment.

Although the project was originally scheduled to finish in 2006, we have plans to continue the project at no additional cost for one year with the goal of enhancing the clinical relevance of the research results through the incorporation of PET/CT and other new PET imaging technologies. A plan to install two new PET/CT devices at the contract performing organizations in 2007 has given us the opportunity to implement this change in project scope. Technological advancements that will be incorporated include hybrid PET/CT imaging, time-of-flight imaging, and dynamic (list-mode) data acquisition. The use of a hybrid PET/CT device will allow us to continue to develop FCH PET/CT for prostate radiation therapy planning applications, while the ability to perform dynamic image acquisitions will allow us to refine our existing imaging protocol in support of the current FDA IND application for fluorocholine. The accrual of research subjects will resume after installation of the new PET/CT systems in 2007. A detailed immunohistochemical analysis of all specimens, as described in the original statement of work, is also planned once the study accrual goal has been met. In this manner, the potential clinical impact of this project will be preserved by keeping pace with the state of the art in PET imaging technology.

REFERENCES

1. Basillote JB, Armenakas NA, Hochberg DA, Fracchia JA. Influence of prostate volume in the detection of prostate cancer. *Urology.* 2003;61(1):167-171.
2. Naughton CK, Miller DC, Mager DE, Ornstein DK, Catalona WJ. A prospective randomized trial comparing 6 versus 12 prostate biopsy cores: impact on cancer detection. *J Urol.* 2000;164(2):388-392.
3. el-Gabry EA, Halpern EJ, Strup SE, Gomella LG. Imaging prostate cancer: current and future applications. *Oncology (Huntingt).* 2001;15(3):325-336; discussion 339-342.
4. Lim J, Dorman E, Cabral C. Automated Production of[18F]FECh and [18F]FCH: Preparation and Use of [18F]Fluoroalkane Sulfonates and Fluoroalkylation Agents. *J. Label Compd Radiopharm.* 2003;46(S1):S403.
5. Schmid DT, John H, Zweifel R, et al. Fluorocholine PET/CT in patients with prostate cancer: initial experience. *Radiology.* 2005;235(2):623-628.
6. Kwee SA, Wei H, Sesterhenn I, Yun D, Coel MN. Localization of primary prostate cancer with dual-phase 18F-fluorocholine PET. *J Nucl Med.* 2006;47(2):262-269.
7. Kwee SA, Coel MN, Lim J, Ko JP. Combined use of F-18 fluorocholine positron emission tomography and magnetic resonance spectroscopy for brain tumor evaluation. *J Neuroimaging.* 2004;14(3):285-289.
8. Kwee SA, Coel MN, Lim J, Ko JP. Prostate cancer localization with 18fluorine fluorocholine positron emission tomography. *J Urol.* 2005;173(1):252-255.
9. Mullerad M, Hricak H, Kuroiwa K, et al. Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. *J Urol.* 2005;174(6):2158-2163.
10. Martorana G, Schiavina R, Corti B, et al. 11C-choline positron emission tomography/computerized tomography for tumor localization of primary prostate cancer in comparison with 12-core biopsy. *J Urol.* 2006;176(3):954-960; discussion 960.
11. Surti S, Karp JS, Popescu LM, Daube-Witherspoon ME, Werner M. Investigation of time-of-flight benefit for fully 3-D PET. *IEEE Trans Med Imaging.* 2006;25(5):529-538.

APPENDIX 1: Statement of Work (Revised July 2006)

Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography

Task 1. Study Preparation, Months 1-4:

a. Finalize research protocol and study-specific forms.

b. Obtain institutional review board (IRB) approval of study protocol and consent form at project sites: Tripler Army Medical Center (TAMC), Queen's Medical Center (QMC), and the Armed Forces Institute of Pathology (AFIP).

c. Orient all study personnel on protocol and methods.

Task 2. Subject Recruitment and Data Collection, Months 4-20:

a. Begin subject recruitment at TAMC and QMC. A total of 25 subjects will be recruited from both sites over a 16 month period.

b. Subjects will undergo whole-body F-18 FCH PET or PET/CT scanning to acquire images of the prostate gland.

c. Subjects not undergoing PET/CT will undergo a separate CT at QMC.

d. Following surgery, the prostatectomy specimens will delivered to AFIP for processing and analysis. Analysis procedures include surgical histopathology and immunohistochemical staining for the Ki-67 antigen. The data will be recorded on study-specific pathology forms.

e. All data will be entered into a study database for analysis.

Task 3. Data Analyses, Months 6 – 20:

a. PET or PET/CT image analysis will be performed by two physicians.

b. Collected data will be analyzed and correlated in periodic interim analyses. Interim results will be summarized in annual reports.

Task 4. Final Analyses/Reporting and Design of Secondary Studies, Months 20-24:

a. Finalize analysis of data and summarize results as stated in the specific aims.

b. Prepare final report and manuscripts for publication.

c. Design secondary studies using the collected data.

APPENDIX 2: Supplementary Data

Table 2: Sextant Malignancy and Maximum Standardized Uptake Value (SUVMax)

Subject	Sextant	Malignant (1=yes, 0=no)	Tumor > 0.5 cm (1=yes, 0=no)	Sextant SUVMax
1	RB	1	1	6.9
	LB	1	1	6.6
	RM	1	1	6.5
	LM	1	1	5.8
	RA	1	1	4.9
	LA	0	0	4.9
2	RB	1	1	10.3
	LB	1	1	11.3
	RM	1	1	9.8
	LM	1	1	10.0
	RA	1	1	10.4
	LA	1	1	7.8
3	RB	0	0	3.2
	LB	1	1	4.6
	RM	0	0	3.1
	LM	1	1	4.9
	RA	0	0	2.2
	LA	1	1	3.8
4	RB	0	0	2.6
	LB	1	1	3.5
	RM	0	0	1.7
	LM	1	1	2.7
	RA	1	0	2.2
	LA	1	0	2.5
5	RB	0	0	3.4
	LB	0	0	3.3
	RM	0	0	3.5
	LM	0	0	3.7
	RA	1	0	4.1
	LA	1	0	3.6
6	RB	1	1	5.4
	LB	0	0	3.3
	RM	1	1	5.8
	LM	0	0	3.5
	RA	0	0	2.9
	LA	0	0	2.6
7	RB	0	0	2.3
	LB	1	0	3.2
	RM	0	0	2.5
	LM	0	0	2.2
	RA	1	0	3.2
	LA	1	0	3.0
8	RB	1	1	4.0
	LB	0	0	3.0
	RM	1	1	4.5
	LM	0	0	3.9
	RA	1	1	4.4
	LA	0	0	4.1
9	RB	1	1	4.4
	LB	1	1	6.5
	RM	1	1	5.6
	LM	1	1	6.9
	RA	1	1	4.0
	LA	1	1	4.7
10	RB	1	1	5.8
	LB	0	0	5.3
	RM	1	1	7.0
	LM	1	1	6.8
	RA	1	1	5.7
	LA	1	1	5.9
11	RB	1	1	4.1
	LB	1	1	4.4
	RM	1	1	6.5
	LM	1	1	7.2
	RA	1	1	7.3
	LA	1	1	6.5
12	RB	1	1	6.9
	LB	1	1	7.0
	RM	0	0	4.5
	LM	1	1	7.2
	RA	0	0	4.2
	LA	1	1	5.7
13	RB	0	0	6.5
	LB	0	0	6.5
	RM	1	1	7.0
	LM	1	1	7.3
	RA	1	1	6.1
	LA	1	1	7.0
	RB	0	0	5.4
14	LB	1	0	6.6
	RM	1	0	6.4
	LM	1	0	6.7
	RA	0	0	6.4
	LA	1	0	6.6
15	RB	0	0	5.5
	LB	0	0	4.9
	RM	1	1	7.8
	LM	1	1	6.2
	RA	1	1	6.7
	LA	1	1	7.1

(RB=right base, LB=left base, RM=right mid, LM=left mid, RA=right apex, LA=left apex)

APPENDIX 2: Supplementary Data (Continued)

Table 3: Receiver Operating Characteristic Curve for Sextant SUVmax as a Discriminator for Sextants Containing Malignant Tumors of Any Size

SUVmax	1-Specificity	Sensitivity	True Pos	True Neg	False Pos	False Neg	SUVmax	1-Specificity	Sensitivity	True Pos	True Neg	False Pos	False Neg
11.34	0	0.0164	1	29	0	60	5.4	0.1379	0.6557	40	25	4	21
10.41	0	0.0328	2	29	0	59	5.36	0.1724	0.6557	40	24	5	21
10.33	0	0.0492	3	29	0	58	5.31	0.2069	0.6557	40	23	6	21
9.96	0	0.0656	4	29	0	57	4.94	0.2414	0.6557	40	22	7	21
9.79	0	0.082	5	29	0	56	4.9	0.2414	0.6721	41	22	7	20
7.81	0	0.0984	6	29	0	55	4.89	0.2414	0.6885	42	22	7	19
7.75	0	0.1148	7	29	0	54	4.86	0.2759	0.6885	42	21	8	19
7.33	0	0.1311	8	29	0	53	4.7	0.2759	0.7049	43	21	8	18
7.3	0	0.1475	9	29	0	52	4.56	0.2759	0.7213	44	21	8	17
7.17	0	0.1639	10	29	0	51	4.5	0.2759	0.7377	45	21	8	16
7.15	0	0.1803	11	29	0	50	4.49	0.3103	0.7377	45	20	9	16
7.09	0	0.1967	12	29	0	49	4.4	0.3103	0.7705	47	20	9	14
7.04	0	0.2131	13	29	0	48	4.37	0.3103	0.7869	48	20	9	13
7.01	0	0.2295	14	29	0	47	4.19	0.3448	0.7869	48	19	10	13
6.98	0	0.2623	16	29	0	45	4.12	0.3448	0.8197	50	19	10	11
6.91	0	0.2787	17	29	0	44	4.1	0.3793	0.8197	50	18	11	11
6.9	0	0.2951	18	29	0	43	4	0.3793	0.8525	52	18	11	9
6.87	0	0.3115	19	29	0	42	3.85	0.4138	0.8525	52	17	12	9
6.78	0	0.3279	20	29	0	41	3.81	0.4138	0.8689	53	17	12	8
6.73	0	0.3443	21	29	0	40	3.68	0.4483	0.8689	53	16	13	8
6.68	0	0.3607	22	29	0	39	3.61	0.4483	0.8852	54	16	13	7
6.63	0	0.377	23	29	0	38	3.51	0.4483	0.9016	55	16	13	6
6.58	0	0.3934	24	29	0	37	3.5	0.4828	0.9016	55	15	14	6
6.55	0	0.4098	25	29	0	36	3.48	0.5172	0.9016	55	14	15	6
6.52	0	0.4262	26	29	0	35	3.37	0.5517	0.9016	55	13	16	6
6.51	0.0345	0.4262	26	28	1	35	3.31	0.5862	0.9016	55	12	17	6
6.5	0.0345	0.4426	27	28	1	34	3.3	0.6207	0.9016	55	11	18	6
6.47	0.0345	0.459	28	28	1	33	3.2	0.6207	0.9344	57	11	18	4
6.46	0.0345	0.4754	29	28	1	32	3.17	0.6552	0.9344	57	10	19	4
6.45	0.069	0.4754	29	27	2	32	3.09	0.6897	0.9344	57	9	20	4
6.44	0.069	0.4918	30	27	2	31	3	0.7241	0.9508	58	8	21	3
6.38	0.1034	0.4918	30	26	3	31	2.9	0.7586	0.9508	58	7	22	3
6.17	0.1034	0.5082	31	26	3	30	2.74	0.7586	0.9672	59	7	22	2
6.11	0.1034	0.5246	32	26	3	29	2.63	0.7931	0.9672	59	6	23	2
5.94	0.1034	0.541	33	26	3	28	2.6	0.8276	0.9672	59	5	24	2
5.82	0.1034	0.5574	34	26	3	27	2.5	0.8621	0.9836	60	4	25	1
5.8	0.1034	0.5738	35	26	3	26	2.3	0.8966	0.9836	60	3	26	1
5.78	0.1034	0.5902	36	26	3	25	2.2	0.931	0.9836	60	2	27	1
5.74	0.1034	0.6066	37	26	3	24	2.17	0.931	1	61	2	27	0
5.68	0.1034	0.623	38	26	3	23	2.16	0.9655	1	61	1	28	0
5.6	0.1034	0.6393	39	26	3	22	1.68	1	1	61	0	29	0
5.51	0.1379	0.6393	39	25	4	22	1.68	1	1	61	0	29	0

APPENDIX 2: Supplementary Data (continued)

Table 4: Receiver Operating Characteristic Curve for Sextant SUVmax as a Discriminator for Sextants Containing Malignant Tumors Larger than 0.5 cm in Diameter

SUVmax	1-Specificity	Sensitivity	True Pos	True Neg	False Pos	False Neg	SUVmax	1-Specificity	Sensitivity	True Pos	True Neg	False Pos	False Neg
11.34	0	0.02	1	40	0	49	5.4	0.2	0.72	36	32	8	14
10.41	0	0.04	2	40	0	48	5.36	0.225	0.72	36	31	9	14
10.33	0	0.06	3	40	0	47	5.31	0.25	0.72	36	30	10	14
9.96	0	0.08	4	40	0	46	4.94	0.275	0.72	36	29	11	14
9.79	0	0.1	5	40	0	45	4.9	0.275	0.74	37	29	11	13
7.81	0	0.12	6	40	0	44	4.89	0.275	0.76	38	29	11	12
7.75	0	0.14	7	40	0	43	4.86	0.3	0.76	38	28	12	12
7.33	0	0.16	8	40	0	42	4.7	0.3	0.78	39	28	12	11
7.3	0	0.18	9	40	0	41	4.56	0.3	0.8	40	28	12	10
7.17	0	0.2	10	40	0	40	4.5	0.3	0.82	41	28	12	9
7.15	0	0.22	11	40	0	39	4.49	0.325	0.82	41	27	13	9
7.09	0	0.24	12	40	0	38	4.4	0.325	0.86	43	27	13	7
7.04	0	0.26	13	40	0	37	4.37	0.325	0.88	44	27	13	6
7.01	0	0.28	14	40	0	36	4.19	0.35	0.88	44	26	14	6
6.98	0	0.32	16	40	0	34	4.12	0.375	0.9	45	25	15	5
6.91	0	0.34	17	40	0	33	4.1	0.4	0.9	45	24	16	5
6.9	0	0.36	18	40	0	32	4	0.4	0.94	47	24	16	3
6.87	0	0.38	19	40	0	31	3.85	0.425	0.94	47	23	17	3
6.78	0	0.4	20	40	0	30	3.81	0.425	0.96	48	23	17	2
6.73	0.025	0.4	20	39	1	30	3.68	0.45	0.96	48	22	18	2
6.68	0.025	0.42	21	39	1	29	3.61	0.475	0.96	48	21	19	2
6.63	0.05	0.42	21	38	2	29	3.51	0.475	0.98	49	21	19	1
6.58	0.075	0.42	21	37	3	29	3.5	0.5	0.98	49	20	20	1
6.55	0.075	0.44	22	37	3	28	3.48	0.525	0.98	49	19	21	1
6.52	0.075	0.46	23	37	3	27	3.37	0.55	0.98	49	18	22	1
6.51	0.1	0.46	23	36	4	27	3.31	0.575	0.98	49	17	23	1
6.5	0.1	0.48	24	36	4	26	3.3	0.6	0.98	49	16	24	1
6.47	0.1	0.5	25	36	4	25	3.2	0.65	0.98	49	14	26	1
6.46	0.1	0.52	26	36	4	24	3.17	0.675	0.98	49	13	27	1
6.45	0.125	0.52	26	35	5	24	3.09	0.7	0.98	49	12	28	1
6.44	0.15	0.52	26	34	6	24	3	0.75	0.98	49	10	30	1
6.38	0.175	0.52	26	33	7	24	2.9	0.775	0.98	49	9	31	1
6.17	0.175	0.54	27	33	7	23	2.74	0.775	1	50	9	31	0
6.11	0.175	0.56	28	33	7	22	2.63	0.8	1	50	8	32	0
5.94	0.175	0.58	29	33	7	21	2.6	0.825	1	50	7	33	0
5.82	0.175	0.6	30	33	7	20	2.5	0.875	1	50	5	35	0
5.8	0.175	0.62	31	33	7	19	2.3	0.9	1	50	4	36	0
5.78	0.175	0.64	32	33	7	18	2.2	0.925	1	50	3	37	0
5.74	0.175	0.66	33	33	7	17	2.17	0.95	1	50	2	38	0
5.68	0.175	0.68	34	33	7	16	2.16	0.975	1	50	1	39	0
5.6	0.175	0.7	35	33	7	15	1.68	1	1	50	0	40	0
5.51	0.2	0.7	35	32	8	15	1.68	1	1	50	0	40	0

APPENDIX 3

SCIENTIFIC ABSTRACTS

Abstract 1

Presented at the 54th Annual Kimbrough Urological Seminar, February 2007

TITLE: Comparisons Between Prostate Histopathology and Imaging with 18F-Fluorocholine PET.

AUTHORS: Stack R, Thibault R, Kwee S, Furusato B, Potter K, Coel MN, Sesterhenn I.

PURPOSE: Fluorocholine (FCH) is a synthetic derivative of choline that is being investigated as a potential tumor imaging agent for positron emission tomography (PET). The phosphorylation of FCH by choline kinase (CK), an enzyme commonly over-expressed in malignancy, results in the intracellular trapping of this compound. FCH is labeled with the isotope fluorine-18 (18F-) to allow in-vivo measurements of tissue FCH uptake using PET. The objective of this histopathologic correlation study was to preliminarily assess the accuracy of PET imaging with 18F-FCH for detecting malignancy in the prostate on a sextant basis.

METHOD: Histopathologic analysis was performed on completely embedded whole-mounted prostate specimens from 15 subjects who underwent pre-operative whole-body PET imaging with 18F-FCH prior to radical prostatectomy. Whole body and pelvic PET images were acquired 10 minutes following intravenous administration of 3.3 to 4 Mbq/kg of 18F- FCH. The images were assessed by region of interest analysis to measure the maximum standardized uptake value (SUVmax) within prostate sextants. These measures of uptake were correlated with the results of histopathology to determine the accuracy of FCH PET for detecting malignantly-involved prostate sextants.

RESULTS: The mean age of subjects was 61 years (range 47 to 71 years). Benign prostatic hyperplasia (BPH) or chronic prostatitis was evident in all prostate specimens. Mean weight of the prostate specimens was 50 gm (range 13 to 106 gm). The average total tumor volume was 4.9 cc (range 0.01 cc to 28.7 cc). Sixty-one of 90 prostate sextants contained at least one malignant tumor on analysis of the whole-mounted specimen. In all patients, the sextant demonstrating the highest 18F-FCH uptake contained a malignant tumor on analysis of the whole-mounted specimen. Mean SUVmax in malignant sextants was significantly higher than in benign sextants (6.0 vs. 3.8 respectively, $p < 0.0001$) despite the fact that benign sextants exhibited BPH or prostatitis. The area under the receiver operating characteristic (ROC) curve for detecting malignant sextants on the basis of sextant SUVmax was 0.82. Using an SUVmax greater than 4.0 as the criteria for malignant uptake, the sensitivity and specificity of 18F-FCH PET for sextant diagnosis were 85% and 62% respectively. Sensitivity was affected by the limited ability of PET to detect small tumors: 6 out of 9 false-negative sextants contained tumors with a largest diameter of less than 0.5 cm. No correlation was found between Gleason Score and SUVmax in malignant sextants.

DISCUSSION: Prostate cancer is elusive to conventional diagnostic imaging. In the prostate, attempts to distinguish malignancy have been confounded by the age-associated increase in prevalence of both benign and malignant diseases of the prostate. Using whole prostate histopathology as the gold-standard, we evaluated FCH PET as a means to identify malignant involvement in prostate sextants. Despite the presence of benign disease, FCH PET was able to localize malignant involvement in prostate sextants. However, the resolution of current PET scanners limits the ability to detect smaller tumors. Enhancements in PET/CT instrumentation in the future should improve sensitivity for smaller lesions. By providing an estimate of tumor burden and location, FCH PET may aid in treatment planning and clinical risk stratification for prostate cancer.

Initial Results From a Whole Prostate Histopathologic Correlation Study

Thibault G[1], Stack R[1], Kwee SA[2], Furusato B[3], Potter, K[3], Coel MN[2], Sesterhenn IA[3]
[1]Department of Urology, Tripler Army Medical Center, Tripler, Hawaii
[2]Hamamatsu/Queen's PET Imaging Center, The Queen's Medical Center, Honolulu, Hawaii
[3]Armed Forces Institute of Pathology, Washington DC

Purpose

Fluorocholine (FCH) is a synthetic derivative of choline that is being investigated as a potential tumor imaging agent for positron emission tomography (PET). The phosphorylation of FCH by choline kinase (CK), an enzyme commonly over-expressed in malignancy, results in the intracellular trapping of this compound. FCH is labeled with the isotope fluorine-18 (18F-) to allow in-vivo measurements of tissue FCH uptake using PET. The objective of this histopathologic correlation study was to preliminarily assess the accuracy of PET imaging with 18F-FCH for detecting malignancy in the prostate on a sextant basis.

Materials and Methods

Histopathologic analysis was performed on completely embedded whole-mounted prostate specimens from 15 subjects who underwent pre-operative whole-body PET imaging with 18F-FCH prior to radical prostatectomy. Whole body and pelvic PET images were acquired 10 minutes following intravenous administration of 3.3 to 4 Mbq/kg of 18F- FCH. The images were assessed by region of interest analysis to measure the maximum standardized uptake value (SUVmax) within prostate sextants. These measures of uptake were correlated with the results of histopathology to determine the accuracy of FCH PET for detecting malignantly-involved prostate sextants.

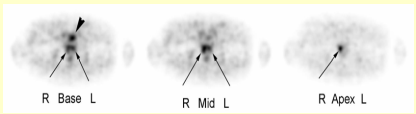


Figure 1: Pre-operative transaxial PET images of the pelvis at the level of the prostate base, mid-section, and apex.. On histopthology, only the left apex did not have malignant involvement. The corresponding sextant on PET demonstrates low FCH uptake, while the other sextants demonstrate high uptake. Note- On the first PET image, the urinary bladder (arrowhead) can be seen as an area of high uptake anterior to the prostate base. This finding is due to normal urinary excretion of FCH and should not be confused with malignancy.

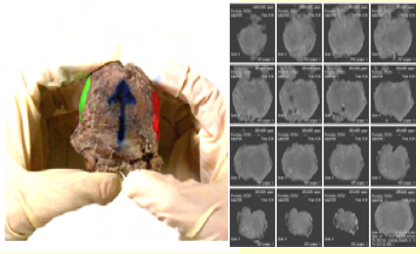


Figure 2: After fixation in formalin, the intact prostate specimen (left) is imaged at 7 tesla using a magnetic resonance microscopy (MRM) scanner. Volumetric MRM data (right) is used to facilitate whole-mounted slice realignment after step-sectioning.

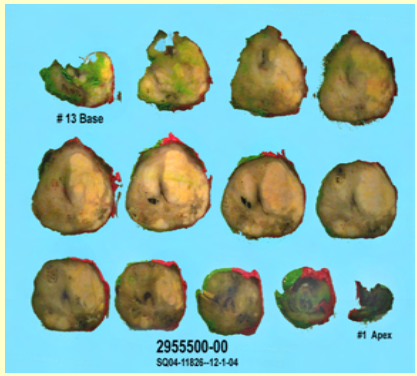


Figure 3: The oriented whole-prostate is cut into 2.2 mm slices. After tissue processing, the slices are embedded in paraffin, sectioned at 4 microns, and whole-mounted on large (50 x 75 mm) glass slides.

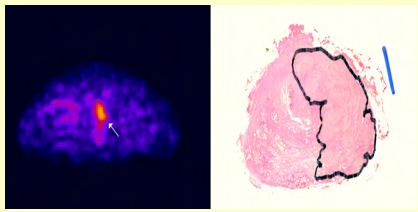


Figure 4: On the transaxial PET image (left), maximum FCH accumulation was localized to the left lobe of the prostate (white arrow). Malignancy limited to the left lobe was later confirmed by H&E light microscopy (right).

Results

The mean age of subjects was 61 years (range 47 to 71 years). Benign prostatic hyperplasia (BPH) or chronic prostatitis was evident in all prostate specimens. Mean weight of the prostate specimens was 50 gm (range 13 to 106 gm). The average total tumor volume was 4.9 cc (range 0.01 cc to 28.7 cc). Sixty-one of 90 prostate sextants contained at least one malignant tumor on analysis of the whole-mounted specimen. In all patients, the sextant demonstrating the highest 18F-FCH uptake contained a malignant tumor on analysis of the whole-mounted specimen. Mean SUVmax in malignant sextants was significantly higher than in benign sextants (6.0 vs. 3.8 respectively, $p < 0.0001$) despite the fact that benign sextants exhibited BPH or prostatitis. The area under the receiver operating characteristic (ROC) curve for detecting malignant sextants on the basis of sextant SUVmax was 0.82. Using an SUVmax greater than 4.0 as the criteria for malignant uptake, the sensitivity and specificity of 18F-FCH PET for sextant diagnosis were 85% and 62% respectively. Sensitivity was affected by the limited ability of PET to detect small tumors: 6 out of 9 false-negative sextants contained tumors with a largest diameter of less than 0.5 cm. No correlation was found between Gleason Score and SUVmax in malignant sextants.

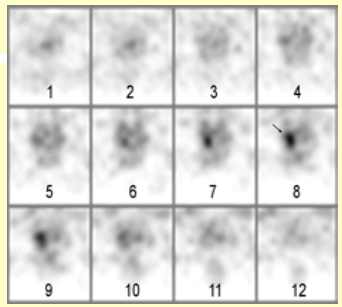


Figure 5: Magnified transaxial PET images of the prostate from base (frame 1) to apex (frame 12). A focus of increased uptake is shown the right mid-portion of the prostate gland (black arrow). Although this 0.5 cm tumor was detectable on PET, most small tumors in this study were not detected.

Discussion and Conclusion

Prostate cancer is elusive to conventional diagnostic imaging. In the prostate, attempts to distinguish areas as malignant have been confounded by the age-associated increase in prevalence of both benign and malignant diseases of the prostate. Using whole prostate histopathology as the gold-standard, we evaluated FCH PET as a means to identify malignant involvement in prostate sextants. Despite the presence of benign disease, FCH PET was able to localize malignant involvement in prostate sextants. However, the resolution of current PET scanners will limit the ability to detect smaller tumors. Enhancements in PET/CT instrumentation in the future should improve the ability to detect smaller lesions. By providing an estimate of tumor burden and location, 18F-FCH PET may aid in treatment planning and clinical risk stratification for prostate cancer.

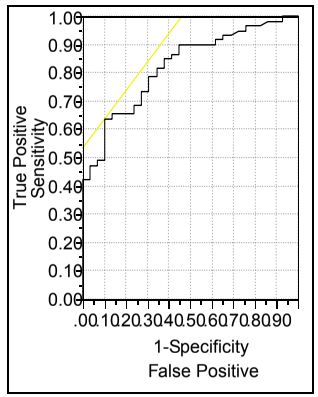


Figure 6: Receiver operating characteristic curve for detecting malignant involvement of prostate sextants on the basis of 18F- FCH uptake.

Acknowledgements

This work was supported by Department of Defense Prostate Cancer Research Program Grant PC04130.

John A. Burns School of Medicine
University of Hawai'i at Manoa

Intensity Modulated Radiation Therapy For Prostate Cancer With Radiation Dose Augmentation Guided By 18F-FCH PET Imaging

Kwee S, Wei H, Sesterhenn I, Yun D, Lederer J, Pang L, Coel M
Hamamatsu/Queen's PET Imaging Center, Queen's Medical Center, Honolulu, Hawaii
University of Hawaii College of Engineering, Honolulu, HI
University of Hawaii School of Medicine, Honolulu, HI

THE QUEEN'S MEDICAL CENTER
Honolulu, Hawaii

Hamamatsu/Queen's
PET IMAGING CENTER, LLC

Introduction

Inaccurate target assessment can lead to radiation treatment failures and unnecessary radiation burdens on patients. The likelihood of tumor control following external beam radiation therapy for organ-confined prostate cancer is directly related to the total radiation dose that can be delivered to the prostate [1]. Radiation doses to the prostate have conventionally been limited by the tolerance of the bowel and bladder to the toxic effects of ionizing radiation. Advanced conformal methods of radiation delivery have provided a potential means to overcome this limitation by selectively applying higher radiation doses to smaller targets with the assumption that such targets may benefit from receiving a higher dose of radiation. PET scanning using the choline derivative Fluorine-18 fluorocholine (18F-FCH) has demonstrated the potential to localize malignant areas within the prostate gland [2,3]. Based on the premise that increased 18F-FCH uptake reflects a higher degree of malignancy, we investigated the feasibility of delivering an augmented radiation dose of at least 90 Gy to a biological target volume (BTV) which encompasses the areas of greatest 18F- FCH uptake on prostate PET images, while still achieving a therapeutic dose of 76 Gy to the remainder of the planning target volume, and while maintaining a tolerable dose to the surrounding normal tissues.

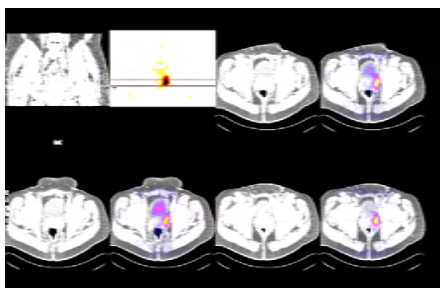


Figure 1: Co-registered CT and 18F-FCH PET images of the prostate. The area demonstrating highest FCH uptake in the left prostatic lobe was also the only region confirmed by histopathologic sampling to be malignant.

Materials and Methods

A conventional intensity modulated radiation therapy (IMRT) plan was designed to deliver a fractionated dose of 1.8 Gy/day to the entire prostate to achieve a total dose of 75.6 Gy. An experimental treatment plan was designed to encompass the BTV within a 2.25 Gy/day isodose line, while the prostate planning target volume was encompassed by a standard 1.8 Gy/day isodose line. The BTV was defined by 18F-FCH PET imaging of the prostate using a value of greater than two standard deviations above the mean standardized uptake value (SUV) of contralateral, histopathologically benign, prostate tissue as the isovalue threshhold (Figure 1). The experimental goal was to prescribe to the BTV a minimum total dose of 90 Gy. Dose constraints to the rectum and bladder were selected to achieve an RTOG Grade 2 complication rate of less than 10% [4]. Dose volume histograms were used to compare the radiation dose to the rectum and other adjacent normal tissues under these two plans (Figure 3).

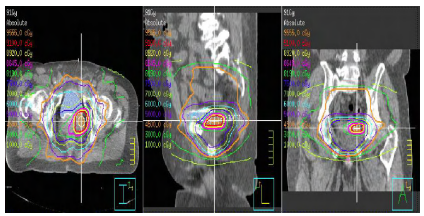


Figure 2: IMRT Plan analysis. Color-coded isodose threshhold lines are superimposed over the planning CT images.

Results

The prostate volume was 62cc and the BTV volume was 14cc. In the conventional plan, a minimum dose of 76 Gy was prescribed to the prostate. In the experimental plan, a minimum dose of 91 Gy was prescribed to the BTV, while achieving a minimum dose of 76 Gy to the remainder of the prostate (Figure 2).

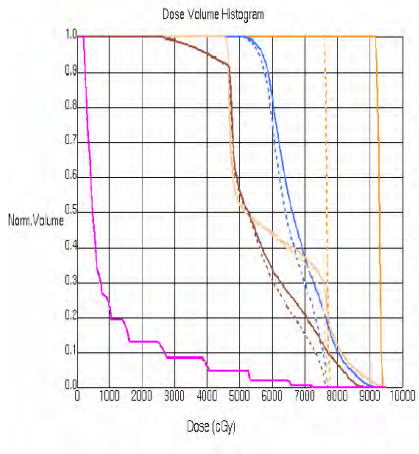


Figure 3: Dose volume histogram comparing conventional (dashed line) and experimental (solid line) treatment plans. Radiation doses to prostate (yellow), rectum (brown), and bladder (blue) are plotted as a function of the normalized tissue volume.

Both plans met desired dose constraints, with less than 20% of the rectal wall receiving 70 Gy or higher dose and less than 25% of the bladder volume receiving 75 Gy or higher dose (Figure 3).

Conclusion

It is feasible to plan IMRT with selective escalation of the radiation dose to high-risk intraprostatic targets while achieving a therapeutic dose to the remainder of the prostate and a tolerable dose to surrounding normal structures. In selected patients, target volumes within the prostate can be defined on the basis of 18F-FCH PET imaging.

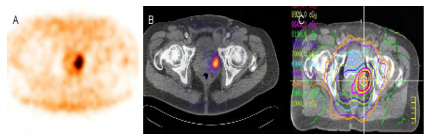


Figure 4: Summary of the experimental treatment plan: The biological target was identified by increased 18F-FCH uptake on PET (A), localized for treatment planning by registered PET/CT (B), and applied potentially as a target volume for dose augmentation to > 91Gy while treating the remainder of the prostate with a conventional 76 Gy dose (C).

Acknowledgements

The work was supported in part by NIH Grant R41CA110121 and Department of Defense Prostate Cancer Research Program Grant PC04130.

References

[1] Lyons JA, Kupelian PA, Mohan DS, Reddy CA, Klein EA. Importance of high radiation doses (72 Gy or greater) in the treatment of stage T1-T3 adenocarcinoma of the prostate. *Urology*. 2000;55(1):85-90.

[2] Kwee SA, Coel MN, Lim J, Ko JP. Prostate cancer localization with 18fluorine fluorocholine positron emission tomography. Journal of Urology. 2005 Jan;173(1):252-5.

[3] Kwee SA, Wei H, Yun D, Sesterhenn I, Coel MN. Localization of Primary Prostate Cancer with Dual-phase 18F-Fluorocholine PET. Journal of Nuclear Medicine. 2006 Feb; 47: 262-269.

[4] Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1257-1280.

Abstract 4

Comparison between 2D and 3D prostate PET imaging. V. Kohli*, S. Kwee and M. Coel; Hamamatsu/Queen's PET Imaging Center, Queen's Medical Center, Honolulu, Hawaii. Presented at the 53rd Annual Meeting of the Society of Nuclear Medicine/ San Diego, CA. June 9-13 2006. J. Nucl. Med., May 2006; 47: 370P.

Objectives: Due to its high tumor metabolism and a long radioactive life, F-18 fluorocholine(FCH) is a promising PET probe for prostate cancer. However, the activity in the bladder can be up to four times as that in the prostate and the scattered radiation from the bladder can result in poor visualization of the tumor in the prostate. The objective of this study was to apply Monte Carlo simulation to systematically compare 2D and 3D acquisitions for prostate imaging in terms of noise characteristic, quantitative accuracy and visualization. With Monte Carlo simulation the history of each photon is known, and therefore the true, random and scattered coincidences can be isolated. This can be used in the noise equivalent count rate(NECR) calculations. NECR has been shown to have a direct link to noise in the image. GATE(Geant4 application for tomographic emission) is a Monte Carlo based simulation package with ability to simulate the image formation process in a wide range of tomographic systems.

Methods: GATE was used to simulate an HR+(CTI/Siemens) scanner. A water filled cylinder of radius 12cm and height 15cm was placed at the center of the scanner. Two spheres of radii 2cm(prostate) and 3cm(bladder) respectively were placed at the center and axially offset from the center by 5cm. To replicate a typical scan with F-18 FCH, the bladder to prostate concentration was kept at 4:1. 2D and 3D simulations were performed for 6.2 minutes with .25μCi/cc of F-18 in the prostate. Since, the dose limit on the injected activity is much higher in 2D acquisitions, the 2D simulations were also performed for prostate activity concentration of .5μCi/cc and .75μCi/cc of F-18. NECR was calculated for both 2D and 3D. After correcting for both random and attenuation, the projection data was reconstructed with filtered back projection using software for tomographic imaging reconstruction(STIR). An ellipsoid region of interest of dimensions 2cmx2cmx2cm was drawn on the prostate part of the reconstructed images. The normalized standard deviation(NSD) was found by dividing the standard deviation by the mean of the reconstructed image counts.

Results: For .25μCi/cc activity in the prostate the NECR for 3D and 2D acquisitions were 8647 counts per sec (cps) and 3547 cps and the NSD for 3D and 2D acquisitions were .11 and .44 respectively. For 2D acquisition with prostate activity concentration of .5μCi/cc and .75μCi/cc, the NECRs were 6839 cps and 10031 cps respectively and NSDs were .31 and .24 respectively.

Conclusions: For the same activity concentration, 3D exhibited better noise characteristics. By increasing the activity concentration in 2D, the noise performance improved. The future work will involve 1) validation of our simulations with real phantom experiments 2) comparison between 2D and 3D in terms of resolution recovery and noise performance for a prostate lesion.

Abstract 5

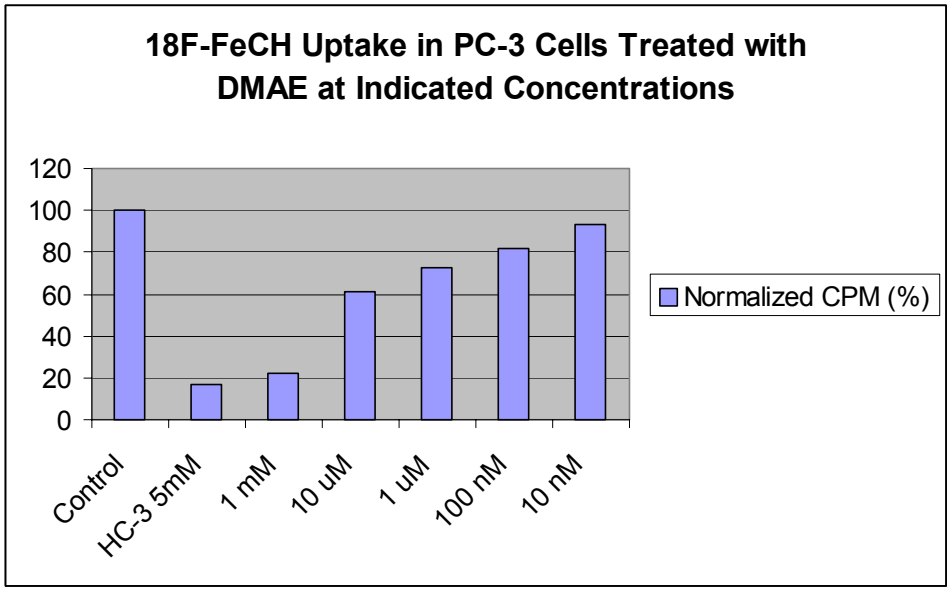
Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study. Kwee S, Thibault G, Stack R, Furusato B, Coel M, Sesterhenn I. Queen's Medical Center, Honolulu, Hawaii. Tripler Army Medical Center. Armed Forces Institute of Pathology. Presented at the 53rd Annual Meeting of the Society of Nuclear Medicine/ San Diego, CA. June 9-13 2006. J. Nucl. Med., May 2006; 47: 459P.

OBJECTIVE: A method for localizing malignancy in the prostate gland may have clinical value as an adjunct for targeted biopsy or treatment. The objective of this preliminary histopathologic correlation study was to determine whether PET imaging with fluorine-18 fluorocholine (18F-FCH) can be used to localize malignancy in the prostate gland. METHOD: Histopathologic analysis was performed on completely embedded whole-mounted prostate specimens from eleven subjects who underwent whole-body PET imaging with 18F-FCH prior to radical prostatectomy. PET images of the prostate were acquired 10 minutes following intravenous administration of 3.3 to 4 Mbq/kg of 18F- FCH. The images were analyzed by region of interest analysis to measure the maximum standardized uptake value (SUVmax) corresponding to prostate sextants. These measures of uptake were correlated with the results of histopathology to determine the accuracy of 18F-FCH PET for detecting malignancy in prostate sextants. RESULTS: The average total tumor volume was 6.5 cc (range 0.5 cc to 28.7 cc). Forty of 60 prostate sextants contained at least one tumor on analysis of the whole-mounted specimen. The mean SUVmax in malignant sextants was significantly higher than in benign sextants (6.6 vs. 5.0 respectively, $p < 0.05$). In all patients, the sextant with the highest 18F-FCH uptake demonstrated carcinoma on analysis of the whole-mounted specimen. The area under the ROC curve for detecting malignant sextants on the basis of sextant SUVmax was 0.76. Using an SUVmax greater than 5.7 as the definition of malignant uptake, the sensitivity and specificity of 18F-FCH PET for sextant diagnosis were 80% and 70% respectively. Four of 8 false-negative sextants contained only tumors smaller than 0.5 cm in greatest dimension. No correlation between Gleason Score and SUVmax in malignant sextants was found in this limited patient series. CONCLUSION: PET imaging with 18F-FCH shows promise for identifying the dominant areas of malignancy within the prostate. However, small volumes of tumor may not be detectable on the basis of measured 18F-FCH uptake.

Abstract 6

Dimethylaminoethanol Reduces 18F-Fluoroethylcholine Uptake in Prostate Cancer Cells.
Kwee S, Lim J, Turner H, Wakano C, Coel MN**.** Presented at the 53rd Annual Meeting of the Society of Nuclear Medicine/ San Diego, CA. June 9-13 2006. J. Nucl. Med., May 2006; 47: 425P.

BACKGROUND: The fluorine-18 (18F-) labeled choline analogs 18F- fluorocholine (FCH) and 18F-fluoroethylcholine (FeCH) are promising PET imaging probes that have demonstrated increased uptake in prostate carcinoma. Synthesis of these compounds can be achieved through alkylation reactions with dimethylaminoethanol (DMAE). However, DMAE is a competitive inhibitor of the high-affinity choline transporter and may reduce cellular uptake of choline radiotracers. The purpose of this experiment was to evaluate the effect of DMAE on in-vitro 18F-FeCH uptake in prostate cancer cells. METHOD: 18F-FeCH was synthesized by fluorination of ethylene ditosylate with 18F, followed by alkylation of the labeled intermediate, 18F- fluoroethylene tosylate, with DMAE. Purification of the final product was performed using either a Silica or Accell (Waters Corporation, Milford MA) Sep-Pak, resulting in removal of DMAE. PC-3 prostate cancer cells were seeded onto 12-well plates and incubated for 3 days in a humidified CO2 environment until 90% confluence was reached. On the day of the experiment, cells in replicate wells were treated with 0.01 uM to 1 mM of DMAE. Control wells consisted of cells treated with 5mM of hemicholinium-3 (HC-3), a potent inhibitor of choline uptake, or no additive. The cells were incubated for 1.5 hours following addition of purified 18F-FeCH to the wells. Cells were harvested, washed 3 times in phosphate buffered saline, and counted for 18F activity using a gamma counter. Measured uptake was expressed as the percentage of radioactivity relative to untreated control cells and normalized to cell count. RESULTS: Radiochemical purity was > 99%. Concentrations of DMAE in preparations of 18F-FeCH ranged from 5 uM to 50 uM. Uptake of 18F- FeCH in cells treated with DMAE decreased in a dose-dependent fashion (Figure 1). Uptake ranged from 80% of control with the addition of 0.1 uM DMAE to 22% of control with the addition of 1 mM DMAE. Inhibition of choline transport/phosphorylation by HC-3 resulted in 18F-FeCH uptake that was 17% of control. CONCLUSION: DMAE, at concentrations present in some 18F-FCH and 18F-FeCH preparations, can reduce in-vitro radiotracer uptake by prostate cancer cells. In-vitro assessments of choline radiotracer uptake should control for inhibition by DMAE. Further study is needed to determine whether similar effects may occur in-vivo.



APPENDIX 4:

Curriculum Vitae of Principal Investigator

Attached on the next 5 pages

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Sandi Alexander Kwee (DOB 8/3/1969)	Principal Investigator Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Carnegie Mellon University, Pittsburgh, PA	B.S.	1987-1991	Electrical Engineering
University of Pittsburgh, Pittsburgh, PA	M.D.	1992-1996	Medicine
University of Hawaii Residency Program, Honolulu, HI		1996-1999	Internal Medicine
University of Washington, Seattle, WA		2000-2002	Nuclear Medicine/PET

CITIZENSHIP: U.S.A

PROFESSIONAL EXPERIENCE

1988-1991	Operations Research Programmer, PPG Industries & Department of Economics, Carnegie Mellon University, Pittsburgh, PA
1991-1992	Research Assistant, Neurobehavioral Studies Program, Western Psychiatric Institute and Clinic, Pittsburgh, PA
1996-1999	Internship and Residency, University of Hawaii Internal Medicine Residency Program, Honolulu, HI
1999-2000	Physician, Internal Medicine and Urgent Care, Waianae Coast Comprehensive Health Center, Waianae, HI
1999-present	Medical Staff, The Queen's Medical Center, Honolulu, HI
1999-2000	Medical Staff, Saint Francis Medical Center, Ewa Beach, HI
2000-2002	Fellow, Nuclear Medicine and PET, University of Washington, Seattle, WA
2001-2002	Staff Physician, Emergency Department, Department of Veterans Affairs-Puget Sound Health Care System, Seattle, WA
2001-2003	Medical Officer, Seattle Division- Department of Veterans Affairs, Puget Sound Health Care System, Seattle, WA
2002-2004	Research Fellow, The Queen's Medical Center, Honolulu, HI
2004-2005	Research Associate, The Queen's Medical Center, Honolulu, HI
2004-present	Assistant Professor, Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2005-present	Research Director, Hamamatsu/Queen's PET Imaging Center, Honolulu, HI

POSITIONS

2003-2005	Member, Brain Imaging Council, Society of Nuclear Medicine, Term 2003-2005.
2004-present	Assistant Professor, Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Clinical Assistant Professor, Department of Geriatric Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI
2004-present	Member, Cancer Committee, The Queen's Medical Center, Honolulu, HI
2005-present	Member, University of Hawaii, Cooperative Institutional Review Board (IRB)
2005-present	Associate Member, University of Hawaii Cancer Research Center Clinical Sciences Program

CERTIFICATION

1999 American Board of Internal Medicine
2002 American Board of Nuclear Medicine
2004 Certification Board of Nuclear Cardiology

HONORS AND AWARDS

Research Scholarship in Neuropsychiatry, University of Pittsburgh Medical Center, 1991

Medical Student Research Excellence Award, University of Pittsburgh School of Medicine, 1993.

Scientific Presentation Award, Annual Straehley Symposium, Kaiser Foundation, November 1997.

Invited Reader, Japan-US Joint Film Reading Conference. 41st Annual Meeting of the Japanese Society of Nuclear Medicine, October 2001.

Residency Award, Asa Seeds Award (Nuclear Medicine), University of Washington, 2002

PROFESSIONAL MEMBERSHIPS

2005-present Society for Molecular Imaging
2004-present American Society of Nuclear Cardiology
2000-present Society of Nuclear Medicine
1996-present American College of Physicians
1996-present American Medical Association
1996-present Hawaii Medical Association
1994-1996 Society of Neuroscience
1991-1996 IEEE

PEER- REVIEWED PUBLICATIONS

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR: PET studies of voluntary saccadic eye movements and spatial working memory. *Schizophrenia Research* 1995 April;15(1,2):100

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol. 1996 Jan;75(1):454-68.

Kwee SA., Ka'anehe L. Occupational Exposures Among University of Hawaii Medical Students. Hawaii Medical Journal. 1999 Feb; 58(2):21-23.

Kwee SA. Minoshima S. A Measure of Functional Reserve Predicts Cognitive Decline in Alzheimer's Disease. J Nucl Med 2001 May; 42(5 Suppl):60-61.

Kwee SA. Nuclear Medicine Training in the United States. KAKU IGAKU (Jpn J Nucl Med) Volume 38, No. 5, 2001.

Liu K. Kwee SA. Demographic, Treatment, and Survival Patterns for Native Hawaiians with Lung Cancer Treated at a University Affiliated Medical Center from 1995 to 2001. Pacific Health Dialog. 2004 September. 11(2): 139-145.

Kwee SA. Coel MN. Lim J. Ko JP. Combined Use of F-18 Fluorocholine PET and Magnetic Resonance Spectroscopy for Brain Tumor Evaluation. Journal of Neuroimaging. 2004 July. 14(3): 285-289.

Kwee SA, Coel MN, Lim J, Ko JP. Sextant Localization of Prostate Cancer with F-18 Fluorocholine Positron Emission Tomography. J Nucl Med May 2004. 45(5 Suppl) : 397

Lum J, Coel M, Kwee SA. A Comparison of Nepro® supplement to cholecystokinin infusion for cholescintigraphy. Clinical Nuclear Medicine.

Kwee SA, Coel MN, Lim J, Ko JP. Prostate cancer localization with 18fluorine fluorocholine positron emission tomography. Journal of Urology. 2005 Jan;173(1):252-5.

Kwee SA, Wei H, Yun D, Sesterhenn I, Coel MN. Localization of Primary Prostate Cancer with Dual-phase 18F-Fluorocholine PET. Journal of Nuclear Medicine. 2006 Feb; 47: 262-269.

Kwee SA, Ko JP, Jiang CS, Watters M, Coel MN. Evaluation of MRI Enhancing Solitary Brain Lesions Using Fluorine-18 Fluorocholine Positron Emission Tomography. Radiology. 2006 –accepted for publication.

Kwee SA. et al. Oncologic Imaging with Fluorine-18 Labeled Choline Derivatives. Seminars in Nuclear Medicine. 2007 –accepted for publication.

ORAL PRESENTATIONS

Kwee SA. *Frontal Lobe Control of Eye Movements*. Scientific Symposium, University of Pittsburgh School of Medicine, 1994.

Sweeney JA, Mintun MA, Carl MR, Kwee S, Steinkopf MB, Rosenberg DR. A positron emission tomography study of voluntary saccadic eye movements.: Society for Neuroscience Abstracts, 1994 Nov;20:107.10

Ka'anehe L, Kwee SA. *Occupational Exposures Among Medical Students*. 28th Annual Straehley Symposium, Kaiser Foundation, Honolulu, HI. November 1997.

Ka'anehe L, Kwee SA. *Occupational Exposures and Knowledge of Universal Precautions Among Medical Students*. American College of Physicians Hawaii Chapter Scientific Meeting, March 1998.

Kwee SA, Minoshima S, Kuhl DE. *Measurement of Functional Reserve Predicts Cognitive Decline in Alzheimer's Disease.* Neurosciences Session. Society of Nuclear Medicine 48th Annual Meeting, June 2001.

Kwee SA, Minoshima S. *Japan-US Joint Film Reading Conference. 41st Annual Meeting of the Japanese Society of Nuclear Medicine, October 2001.*

Kwee SA. *Sodium Iodide Symporter: Target for Novel Anti-Cancer Therapies*. Lecture, Asa Seeds Award 2002. University of Washington Medical Center, February 2002.

Kwee S. Dakhal S. *Distribution of Non-Small Cell Lung Cancer in Hawaii: 1996-2001*. Hawaii Chapter American College of Physicians-American Society of Internal Medicine 2003 Chapter Scientific Meeting.

Bhan U, Kwee S. *Thyroid Scan Acquisition Time as a Marker of Thyroid Hyperfunction*. Hawaii Chapter American College of Physicians-American Society of Internal Medicine 2003 Chapter Scientific Meeting.

Lum J, Kwee S. *New Method in Dynamic Cholescintigraphy*. Hawaii Chapter American College of Physicians-American Society of Internal Medicine 2003 Chapter Scientific Meeting.

Liu D, Kwee S. *Demographic and Survival Patterns for Native Hawaiians with Lung Cancer: 1995-2001.* Kamehameha Schools Research Conference on the Education and Well-being of Hawaiians. 2003

Kwee S. *Producing Quality PET Scans: Optimizations and Protocols*21st Annual Conference. Pacific Northwest Chapter, Society of Nuclear Medicine. Honolulu, HI. 2004.

Kwee S, Ko JP, Coel M. *Use of F-18 Fluorocholine PET and Magnetic Resonance Spectroscopy for Brain Tumor Evaluation.* The 10th Conference of Peace through Mind Brain Science. February 25 – February 27, 2004, Hamamatsu City, Japan.

Kwee S, Lim J, Ko JP, Coel M. *Sextant Localization of Prostate Cancer with F-18 Fluorocholine Positron Emission Tomography.* Scientific Paper Presentation: Prostate Cancer. 51st Annual Meeting. Society of Nuclear Medicine. Philadelphia PA. 2004.

Tay K Dhakal S, Kwee S *Lung Cancer Staging with 18F-Fluorodeoxyglucose Positron Emission Tomography: Effect on Survival..* American College of Physicians: Hawaii Chapter Meeting 2005. Honolulu, HI. March 2005.

Brown, J. Haley A. Kwee S. *Acute Fever and headache in a 22-year-old man with a history of chronic glomerulonephritis and splenectomy: A CPC.* University of Hawaii Department of Medicine Grand Rounds. January 31, 2006.

Kwee S. *Fluorine-18 Labeled Choline Derivatives for Brain Tumor PET Imaging.* The Eleventh Conference of Peach through Mind-Brain Science. Research Foundation for Opto-Science and Technology. Ministry of Education, Culture, Sports, Science and Technology, Japan. Shizuoka Prefecture. February 20-22, 2006.

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Differentiation Between High-Grade Gliomas and Solitary Brain Metastases: Tumoral and Peritumoral Assessment with Fluorine-18 Fluorocholine Positron Emission Tomography.* Society of Molecular Imaging Annual Meeting, August 2006.

G. Thibault, R. Stack, S. A. Kwee, B. Furusato, M. Coel and I. Sesterhenn. *Initial Results From a Whole Prostate Histopathologic Correlation Study.*, American Urologic Association – Western Section. Annual Meeting. October 2006.

Yun DY, Kwee SA, Wei H, Coel M. *A Surface Adaptive Region Growing Algorithm for Tumor Localization, Object Reconstruction and Shape Visualization*. IEEE 2006 Nuclear Science Symposium and Medical Imaging Conference. October 2006.

ABSTRACTS

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR *A Positron Emission Tomography Study of Voluntary Saccadic Eye Movements*. Proceedings Society of Neuroscience 24th Annual Meeting, 1994.

Kwee S. *Stage Miration and Non-small Cell Lung Cancer in Hawaii.* North American Association of Central Cancer Registries Annual Conference. June 2003.

Kohli V, Kwee SA, Coel MN. *Comparison between 2D and 3D Prostate PET Imaging.* J. Nucl. Med., May 2006; 47: 370P.

Kwee SA, Turner H, Lim J, Wakano C, Coel M. *Dimethylaminoethanol Reduces 18F-Fluoroethylcholine Uptake in Prostate Cancer Cells.* J. Nucl. Med., May 2006; 47: 425P.

Kwee S, Wei H, Sesterhenn IA, Yun DY, Coel MN. *Intensity Modulated Radiation Therapy For Prostate Cancer With Radiation Dose Augmentation Guided By 18F-FCH PET Imaging.* J. Nucl. Med., May 2006; 47: 457P.

Kwee SA, Thibault G, Stack R, Furusato B, Coel M, Sesterhenn IA. *Cancer Localization in the Prostate with 18F-Fluorocholine PET: Initial Results From a Whole Prostate Histopathologic Correlation Study.* J. Nucl. Med., May 2006; 47: 459P.

Lim J, Kwee S, Cabral C, Turner H, Wakano C, Stokes A, Coel M. *Automated Synthesis and In Vitro Uptake of [18F] Fluoroethylcholine in Prostate Cancer*. Molecular Imaging July-September 2006 5(3).

Kwee S, Ko JP, Jiang CS, Watters M, Lim J, Coel MN. *Fluorine-18 fluorocholine PET Evaluation of Brain Tumor Recurrence Following Radiation Therapy.* Proceedings of the 9th World Congress of Nuclear Medicine and Biology. Seoul, Korea. October 2006.

FEDERAL GRANTS

PC040130 7/2004 – 7/2007
Cancer Localization in the Prostate with F-18 Fluorocholine Positron Emission Tomography
Congressionally Directed Medical Research Programs
Role: Principal Investigator

R41CA110121 9/2004 – 3/2006
Positron Emission Tomography Guided Prostate Biopsy
National Institutes of Health, National Cancer Institute
Role:Co-Investigator

PAST RESEARCH SUPPORT

The Holy Land Foundation, The James and Sally Zukerkorn Foundation, The Queen Emma Research Foundation, Hamamatsu Photonics KK.